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June 27, 2012

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Request for Revision of Regulatory Review Period
PRADAXA® (dabigatran etexilate mesylate)
Docket No. FDA-2011-E-0117

Dear Sir or Madam:

Boehringer Ingelheim Pharma GmbH & Co. KG ("Boehringer Ingelheim"), through undersigned counsel, hereby requests reconsideration and revision of the Determination of Regulatory Review Period published in the Federal Register on May 3, 2012.[1] In accordance with 21 C.F.R. § 60.24(a), the following information is provided:

(1) The Type of Requested Action

For the reasons stated below, Boehringer Ingelheim respectfully requests that the "date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act" be corrected from April 19, 2010 – the date provided in the Federal Register notice – to December 15, 2009. Accordingly, Boehringer Ingelheim requests that FDA recalculate the "regulatory review period" using December 15, 2009, as the date the approval phase began.

(2) The Identity of the Product

PRADAXA® (dabigatran etexilate mesylate) ("Pradaxa") (NDA 22-512), the product that is the subject of the regulatory review period determination, is marketed and sold in the United States by Boehringer Ingelheim Pharmaceuticals, Inc. ("BIPI").

[1] Tab 1, Determination of Regulatory Review Period for Purposes of Patent Extension; Pradaxa, 77 Fed. Reg. 26,289 (May 3, 2012).

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(3) The Identity of the Applicant

Boehringer Ingelheim Pharma GmbH & Co. KG is the Applicant on the Request for Extension of Patent Term.

(4) The FDA Docket Number

The Docket Number for this Determination of Regulatory Review Period is FDA-2011-E-0117.

(5) The Basis for the Requested Revision, Including Any Documentary Evidence

As detailed below – and as claimed in Boehringer Ingelheim's Application for Extension of Patent Term[2] – the date on which the Pradaxa New Drug Application ("NDA") was "initially submitted" to FDA for purposes of determining the regulatory review period under 35 U.S.C. § 156(g)(1)(B) was December 15, 2009.

BIPI submitted the first sequence of documents across several modules of the Pradaxa NDA for rolling review on September 17, 2009.[3] On December 15, 2009, BIPI submitted the final elements of Pradaxa's NDA to complete the rolling submission of the application. FDA commenced its review of the NDA no later than December 15, 2009.

In its May 3, 2012 Federal Register Notice, FDA announced its determination that the Pradaxa NDA was initially submitted on April 19, 2010. The agency provided the following explanation:

> The applicant claims December 15, 2009, as the date the new drug application (NDA) for PRADAXA (NDA 22–512) was initially submitted. However, FDA records indicate that NDA 22–512, received December 15, 2009, was incomplete. FDA refused to file this application and notified the applicant of this fact by letter dated February 12, 2010. The completed NDA was then submitted on April 19, 2010, which is considered to be the NDA initially submitted date.[4]

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[2] Tab 2, Application for Extension of Patent Term, at Exhibit F (Dec. 10, 2010).

[3] BIPI submitted the first sequence of documents for the Pradaxa NDA for rolling review on September 17, 2009. Tab 3, NDA Pre-submission Cover Letter (Sept. 17, 2009). Under FDA's current interpretation, the first submission of a rolling review NDA is not considered to be an "initial submission" that triggers the start of the "approval phase" for purposes of the PTE calculation. However, if FDA revises this interpretation; a court were to overturn FDA's interpretation; or there were any other change in the applicable law governing the start of the approval phase for applications submitted on a rolling basis, Boehringer Ingelheim reserves the right to claim September 17, 2009, as the date the NDA was initially submitted.

[4] Tab 1, Determination of Regulatory Review Period for Purposes of Patent Extension; Pradaxa, 77 Fed. Reg. at 26,290; *see also* Tab 4, Letter from J. Axelrad, FDA to D. Kappos, PTO (Apr. 18, 2012) (providing total length of

There are two problems with this conclusion. The first is that the governing statute, legislative history, and the agency's own regulations provide that it is the date of the *initial submission* of an NDA that triggers the regulatory review period, not the date of subsequent corrections or amendments to that submission, and not the date of filing. The second is that even assuming in some circumstances that an "initial submission" of an NDA is so deficient as to preclude considered review, here, the agency *never stopped* its review of the NDA.

All of the required elements of the NDA were submitted to FDA as of December 15, 2009. Although FDA issued a refuse-to-file ("RTF") letter to BIPI on February 12, 2010, the agency continued to review the NDA. This fact is unambiguously documented in the agency's own written correspondence with BIPI. Because review of the Pradaxa application continued uninterrupted and unabated from December 15, 2009, to the NDA's approval on October 19, 2010, Boehringer Ingelheim respectfully requests that FDA revise the initial submission date from April 19, 2010 to December 15, 2009.

I. STATUTORY AND REGULATORY FRAMEWORK

New human drugs must receive FDA approval before they can be commercially marketed.[5] The process of producing, assembling, and reviewing such large amounts of pre-clinical and clinical data typically takes many years. This lengthy delay substantially reduces the effective terms of patents covering new drugs. In theory, a patent enables exclusive commercial exploitation of an invention from the time the patent is granted until 20 years after the patent application was filed, because the patent grants an inventor the right to exclude competitors from the market.[6] However, patents covering products subject to premarket approval requirements confer much less of a benefit in practice because the regulatory review process may consume significant portions of that exclusive period.

Congress addressed this problem by enacting the Drug Price Competition and Patent Term Restoration Act of 1984 (often referred to as the "Hatch-Waxman Act").[7] Title II of the Hatch-Waxman Act provides that the holder of a patent covering a drug subject to pre-market approval is entitled to a patent term extension ("PTE") to compensate for the period of time the pre-market approval requirement barred commercial marketing of the product. The purpose of Title II of the statute was "to further encourage new drug research by restoring some of the patent term lost while drug products undergo testing and await FDA pre-market approval."[8]

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regulatory review period for Pradaxa).

[5] *See* 21 U.S.C. §§ 331(d), 355(a) (2006).

[6] *See* 35 U.S.C. § 154(a)(2) (2006).

[7] *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[8] *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392, 396 (Fed. Cir. 1990); *see also* H.R. REP. NO. 98-857, pt. 1, at 15 (1984) ("The purpose of Title II of the Bill is to create a new incentive for increased expenditures for research

The length of the patent term extension available under the Hatch-Waxman Act is calculated based on the "regulatory review period" applicable to the new drug. The statute divides that period into two parts, known as a "testing phase" and an "approval phase,"[9] as follows:

> (g) For purposes of this section, the term "regulatory review period" has the following meanings: . . .
>
> (1)(B) The regulatory review period for a new drug, antibiotic drug, or human biological product is the sum of –
>
> (i) the period beginning on the date an exemption under subsection (i) of section 505 . . . became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 351[or] 505 . . ., and
>
> (ii) the period beginning on the date the application was initially submitted for the approved product under section 351[or] subsection (b) of section 505 . . . and ending on the date such application was approved under such section.[10]

Thus, the testing phase ends and the approval phase immediately begins as soon as the marketing application is "initially submitted" to FDA.

The difference between the two phases – testing and approval – is significant. Patent holders receive a "year-for-year matching extension . . . for any time in the drug approval process that the drug spends awaiting a decision by the FDA."[11] Accordingly, the statute provides for an extension equal to the entire period of the *approval* phase.[12] By contrast, the statute limits the extension to only half the length of the *testing* phase.[13] The different treatment of the testing and approval phases means that the date on which an application is "initially

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and development of certain products which are subject to premarket government approval.").

[9] 21 C.F.R. § 60.22(a) (2011) (describing the "testing phase" and the "approval phase" for human drugs).

[10] 35 U.S.C. § 156(g)(1)(B).

[11] H.R. REP. NO. 98-857, pt. 2, at 6 (1984).

[12] *See* 35 U.S.C. § 156(c).

[13] *See* 35 U.S.C. § 156(c)(2). The length of the available extension is also subject to two upper limits. First, no patent term extension may be longer than 5 years. *See* 35 U.S.C. 156(g)(6)(A). Second, an extension may not extend the effective patent term – the period between FDA approval and patent expiration – beyond 14 years. *See* 35 U.S.C. § 156(c)(3).

submitted" is crucial; that date marks the start of the day-for-day extension Congress provided to compensate for the time during which the NDA is under FDA review.

Congress understood the significance of the phrase "initially submitted." In setting the dividing line between the testing and approval phases, the legislature recognized that FDA "might decide it needs additional information or other changes in the application" even after the application is "initially submitted."[14] The House Report on the Hatch-Waxman Act thus specifically explains that Congress chose the term "initially submitted" rather than the term "filed" because "an application is often not considered to be filed, even though agency review has begun, until the agency has determined that no other information is needed."[15]

The House Report also makes clear that an application is "initially submitted" as soon as it contains sufficient information for the FDA to begin its review:

> For purposes of determining the regulatory review period and its component periods, an application for agency review is considered to be "initially submitted" if the applicant has made a deliberate effort to submit an application containing all information necessary for agency review to begin. The Committee recognizes that the agency receiving the application might decide it needs additional information or other changes in the application. As long as the application was complete enough so that agency action could be commenced, it would be considered to be "initially submitted."[16]

FDA's Patent Term Restoration regulations closely track the legislative explanation of the term "initially submitted." In particular, the governing rule states that for "purposes of determining the regulatory review period for any product, a marketing application . . . is *initially submitted* on the date it contains sufficient information to allow FDA to commence review of the application."[17] Thus, FDA may require additional information from the sponsor in support of the application, but this will not affect the "initially submitted" date or the onset of the approval phase.

II. FACTUAL BACKGROUND

Pradaxa is an FDA-approved human drug product indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Boehringer Ingelheim Pharmaceuticals, Inc., an affiliate of Boehringer Ingelheim Pharma GmbH & Co. KG, is the

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[14] *See* H.R. REP. NO. 98-857, pt. 1, at 44.

[15] *Id.*

[16] *Id.*

[17] 21 C.F.R. § 60.22(f) (emphasis in original).

sponsor of the NDA in support of Pradaxa (NDA 22-512).

On August 6, 2003, the investigational new drug application ("IND") for Pradaxa became effective.[18] Prior to the initial submission of the Pradaxa NDA, the agency requested that it be submitted on a "rolling review" basis.[19] The agency indicated to BIPI, in August 2009, that the agency expected to review the NDA on a "priority" basis because the drug represented a significant improvement over existing therapy. However, for the agency to complete its review on a priority basis, the agency believed it needed to begin its review before the full application could be submitted. Thus, the agency made the following request: "In order for us [FDA] to complete our review of your NDA in a timely fashion, we request that you submit each module as you complete it."[20]

On September 17, 2009, BIPI submitted the first sequence of documents across several modules of the marketing application for Pradaxa.[21] On September 30, 2009, BIPI began submitting data for the clinical module of the NDA.[22] BIPI submitted the final elements of the rolling submission, including documents across several previously submitted modules of the NDA, on December 15, 2009. On January 5, 2010, the agency acknowledged that it had received the NDA on December 15, 2009.[23]

On February 12, 2010, FDA's Division of Cardiovascular and Renal Products (the "Division") sent a Refuse-to-File Letter (the "RTF Letter") to BIPI. In its letter, the Division stated that its RTF determination was based on "transcription errors, transposition errors, and auditing errors."[24] In a meeting following the RTF Letter, the agency asked BIPI to conduct a series of "data quality checks," revise the study report for a Phase 3 study of Pradaxa to reflect any findings that were altered as a result of the data checks, and organize the study report "in a manner that facilitates review."[25] No new data were requested and no major omissions from the NDA were identified in the RTF Letter.

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[18] *See* Tab 1, Determination of Regulatory Review Period for Purposes of Patent Extension; Pradaxa, 77 Fed. Reg. at 26,290. Note that Boehringer Ingelheim originally identified August 7, 2003, as the effective date of the IND but accepts the agency's August 6, 2003, date.

[19] Tab 5, Excerpt of Minutes of Aug. 17, 2009 FDA Meeting (issued Sept. 17, 2009), at 3. Under the standard NDA review process, an applicant may presubmit only the chemistry, manufacturing, and controls section of the NDA. 21 C.F.R. § 314.50(d)(1)(iv). Under the "fast track" review process, any component of an application may be presubmitted according to a prearranged schedule. 21 U.S.C. § 356. The agency did not designate Pradaxa as a "fast track" product.

[20] Tab 5, Excerpt of Minutes of Aug. 17, 2009 FDA Meeting at 3.

[21] Tab 3, NDA Pre-Submission Cover Letter (Sept. 17, 2009)

[22] *See id.* at 2.

[23] Tab 6, NDA Acknowledgment Letter, at 1 (Jan. 5, 2010).

[24] Tab 7, RTF Letter, at 1 (Feb. 12, 2010).

[25] Tab 8, Minutes of Feb. 18, 2010 FDA Meeting, at 2 (received Mar. 15, 2010).

Ordinarily, a refusal-to-file decision will immediately terminate review activity on the application. However, in certain cases, the agency may continue with the review of the application while the sponsor works to repair the facial deficiencies that led to the RTF decision. As FDA's longstanding guidance on RTF actions makes clear:

> The agency may, for particularly critical drugs, not use the RTF procedure, even where it could be invoked, ***or might review parts of a refused application if it believes that initiating the full review at the earliest possible time will better advance the public health.***[26]

The Division chose to follow this approach with respect to the Pradaxa NDA. Notwithstanding the RTF determination, the Division specifically stated in its RTF Letter that it would continue its substantive review of the Pradaxa NDA:

> In recognition of the importance of this priority application, we proposed a rolling review. We will, of course, continue our review of parts of your application that are complete and reviewable, such as the chemistry and pharmacology toxicology sections.[27]

The agency followed through on its commitment and continued its substantive review of the NDA after it issued the RTF Letter. For example, just four days after the RTF Letter, the Division's lead Project Manager for the NDA sent BIPI an e-mail with questions from the agency's liver toxicity experts. The email underscores the fact that review of the NDA continued without interruption after February 12, 2010:

> As I mentioned on the phone, ***regardless of the RTF, we are continuing our review of the application.***[28]

Even when FDA concluded its review in October 2010, individual reviewers acknowledged that they had continued their "ongoing" review activities despite the RTF decision:

> The 15-DEC-2009 submission was refused to file (RTF) on 12-FEB-2010 for clinical reasons. ***However, due to the priority / rolling status of the application, the CMC review remained ongoing after the RTF.***[29]

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[26] CDER, NEW DRUG EVALUATION GUIDANCE DOCUMENT: REFUSAL TO FILE 3 (July 12, 1993) (emphasis added).

[27] Tab 7, RTF Letter, at 2 (Feb. 12, 2010).

[28] Tab 9, Email from A. Blaus, FDA Project Manager, to M. Kliewer (Feb. 16, 2010) (emphasis added).

[29] Tab 10, Excerpt of CDER PRADAXA CHEMISTRY REVIEW, ONDQA DIVISION DIRECTOR'S MEMO 1 (emphasis added). Full Chemistry Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000ChemR.pdf.

As shown in section III.C., below, numerous facets of the review were active, and some were even completed, during the period from December 2009 to March 2010.

On April 19, 2010, BIPI resubmitted the Pradaxa NDA. The resubmission included a response to the data quality issues raised in the RTF Letter. In the cover letter that accompanied this submission to the Division, a BIPI Regulatory Affairs Director wrote:

> We have completed the additional data quality checks agreed to during the February 18, 2010 meeting with the Agency. To the extent possible, the deficiencies noted during the initial FDA review and those identified by the quality checks have been corrected. Based on re-analyses of the update[d] data, the primary efficacy and safety conclusions of RE-LY remain unchanged.[30]

On the basis of this submission, FDA agreed to file the NDA and assigned a Prescription Drug User Fee Act goal date for the review of the Pradaxa NDA.[31] FDA approved the application on October 19, 2010.[32]

On December 13, 2010, Boehringer Ingelheim timely submitted an Application for Patent Term Extension to the United States Patent and Trademark Office. The Application requested an extension of U.S. Patent No. 6,087,380 for a period of 1,469 days. Among other relevant dates, Boehringer Ingelheim identified December 15, 2009 – the date on which the full NDA was before the agency – as the date on which the NDA for Pradaxa was initially submitted to FDA. As of this date, BIPI had submitted to FDA all information required for the submission of an NDA under section 505(b)(1) of the Food, Drug, and Cosmetic Act ("FDCA").[33]

FDA, however, declined to accept the December 15, 2009, date as the start of the approval phase for the Pradaxa NDA.[34] According to FDA, the complete NDA was not submitted until April 19, 2010. On May 3, 2012, FDA published formal notice of this decision in the Federal Register.[35]

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[30] Tab 11, NDA Resubmission Sequence 0047 Cover Letter (Apr. 19, 2010).

[31] Tab 12, NDA Acknowledgment Letter (Apr. 27, 2010).

[32] Tab 13, Pradaxa NDA Approval Letter (Oct. 19, 2010).

[33] Tab 2, Application for Extension of Patent Term at Exhibit F.

[34] Tab 4, Letter from J. Axelrad, FDA to D. Kappos, PTO (Apr. 18, 2012).

[35] Tab 1, Determination of Regulatory Review Period for Purposes of Patent Extension; Pradaxa, 77 Fed. Reg. at 26,290.

III. DISCUSSION

The approval phase begins when an NDA is "initially submitted" to FDA. FDA maintains that the NDA must be *complete* to trigger the approval phase, and that the test for completeness is whether the application meets the agency's standard for administrative filing.[36] Under the agency's reading of the statute, an application that is refused filing cannot as a matter of law trigger the start of the approval phase.

That is not a correct reading of the PTE statute or FDA's implementing regulations. There is no language in the statute or regulations that requires the agency to hold applicants to a *filing* standard in order to trigger the start of the approval phase.

To the contrary, Congress has made clear that an "application" is sufficient to trigger the start of the approval phase if it contains enough information to allow the agency to commence review of the NDA. And, the agency itself took the same position when it issued the governing rules under 21 CFR part 60. An "application" is "initially submitted" if it contains sufficient information to allow the agency to commence review.[37] Whether the application may be filed is a separate question – and not one that is required under the statute or the rules.

When the Pradaxa NDA was initially submitted in full on December 15, 2009, the approval period began. It is quite clear that the Pradaxa NDA, as submitted on December 15, 2009, contained sufficient information to allow the agency to commence its review. Indeed, as of that date, the responsible review division, along with several consulting divisions and offices within CDER, had already commenced their review of Pradaxa and, despite the RTF decision, never ceased their review activities.

In short, Pradaxa represents a case in which an application that was refused filing nevertheless was the subject of ongoing review as of the "initial submission" of the NDA. The "approval phase" for PTE purposes thus was triggered no later than December 15, 2009. And, once triggered, the agency has no basis in law to re-start the testing phase or otherwise terminate the approval phase.

A. FDA's Regulatory Review Determination for Pradaxa Conflicts with the Governing Statute

Congress has spoken directly to the core issue presented here.[38] The statute states that the

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[36] *See* 21 C.F.R. § 314.101(a).

[37] 21 C.F.R. § 60.22(f).

[38] *See Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984) ("If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress."). *See also Ranbaxy Laboratories Ltd. v. Leavitt*, 469 F.3d 120, 125-26 (D.C. Cir. 2006) (rejecting, at *Chevron* step one, FDA creation of a regulatory requirement "inconsistent with the

approval phase begins on the date the application for the approved product was "*initially submitted*" under section 505 of the FDCA. The statute does not state that the approval phase should begin at the time that FDA *administratively files* the NDA. Nor does it state that the start of the approval phase is conditioned on whether FDA administratively files the NDA.

The "submission" of an application is an action taken by the sponsor of a new drug product. "Filing" is a formal action taken by FDA. In this instance, Congress clearly chose to mark the line between testing phase and the approval phase based on the action of the sponsor rather than the action of the agency.

Congress in fact was well aware of the distinction between "submission" and "filing." The term "initially submitted," by definition, contemplates further submissions. The House Report on the Hatch-Waxman Act explains that Congress chose the term "initially submitted" rather than "filed" because "an application is often not considered to be filed, ***even though agency review has begun***, until the agency has determined that no other information is needed."[39] The Report makes clear that an application is "initially submitted" as soon as it contains sufficient information for the FDA to begin its review:

> For purposes of determining the regulatory review period and its component periods, an application for agency review is considered to be "initially submitted" ***if the applicant has made a deliberate effort to submit an application containing all information necessary for agency review to begin***. The Committee recognizes that the agency receiving the application might decide it needs additional information or other changes in the application. As long as the application was ***complete enough so that agency action could be commenced***, it would be considered to be "initially submitted."[40]

Thus, Congress specifically rejected the idea of using an administrative "filing" standard as a necessary basis for determining whether a sponsor has "initially submitted" its application.

Instead, Congress made clear, both in the legislative history and the plain language of the statute, that *submission* of an application sufficient to allow the agency to begin its review activities represents the end of the testing phase and the start of the approval phase. The House Report's use of terms such as "sufficient information" and "complete enough" also make it abundantly clear that Congress understood it is possible to begin review of an application before the application meets all of the technical requirements for filing.

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structure of the statute"); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1069 (D.C. Cir. 1998) ("Here, we think that the FDA's interpretation cannot survive analysis under the first step of *Chevron*.").

[39] H.R. REP. NO. 98-857, pt. 1, at 44 (emphasis added).

[40] *Id.* (emphasis added).

FDA's regulatory review determination for Pradaxa, however, reads a filing standard into the statute, despite the plain language of the statute and the clear intent of Congress. In effect, FDA is applying the statute as if it states that the approval phase begins on the date "an application *that meets the agency's filing standard* is initially submitted under section 505(b)." Of course, no such language appears in the statute and, as we have shown, that was clearly not Congress' intent. Rather, Congress chose language that did not require a formal act of the agency. The statute provides, without doubt or ambiguity, that the end of the testing phase and the beginning of the approval phase is based on the sponsor's act of initially submitting an NDA for review.

Congress understood that "an application is often not considered to be filed . . . until the agency has determined that no other information is needed."[41] It is not up to FDA to now second-guess Congress or re-write the statute. Congress did not condition the approval phase on an FDA filing determination. The approval phase begins when the applicant initially submits an application under section 505(b) with sufficient information to allow the agency to begin its review. That plainly was the case here.[42]

B. FDA's Regulatory Review Determination for Pradaxa is in Conflict with the Agency's Own Regulations

FDA's initial decision in the April 19, 2012, letter is not only inconsistent with the statute, it is in conflict with the agency's own regulations. As with the statute, FDA has defined the terms "marketing application" and "initially submitted," for PTE purposes, based on standards distinct from those used to administratively file a new drug application.

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[41] H.R. REP. NO. 98-857, pt. 1, at 44. *See* DONALD O. BEERS, GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS § 4.04[D] (6th ed. 2004) ("It is noteworthy . . . that the date of 'submission' has been chosen rather than the date of 'filing,' as FDA and the courts have interpreted 'filing' of an application to occur only at a point at which *the agency has found the application complete.*") (emphasis added).

[42] In *Wyeth Holding Corp. v. Sebelius*, 603 F.3d 1291 (2010), the Federal Circuit found §156(g) of the PTE statute ambiguous when applied to a new animal drug application ("NADA") submitted for "phased review." Under phased review of an NADA, technical sections of an eventual NADA may be submitted on a rolling basis to an investigational file held at FDA. The *Wyeth* court concluded that the statute does not clearly resolve whether an application has been "initially submitted" if it is provided to FDA in sections over a period of time, and agreed with FDA's interpretation that sending one individual section to FDA in a separate investigational file did not constitute the initial submission of "an application" for purposes of the PTE statute. Rather, for purposes of section 156(g), the court held that an application must contain in one submission all of the categories of information enumerated in the animal drug statute, 21 U.S.C. § 360b(b), for full NADA. *Wyeth*, 603 F.3d at 1298. As the court of appeals explained, "FDA's *first notice that a sponsor believes it has submitted all of the parts* required by § 360b(b) occurs when the sponsor submits an administrative NADA." *Id.* at 1299 (emphasis added). For Pradaxa, all of the statutorily required elements of the application under section 505(b)(1) of the FDCA were initially submitted to FDA as of December 15, 2009. Under *Wyeth*, then, as of December 15, 2009, BIPI had clearly fulfilled the "first notice" requirements of §156(g) when it "initially submitted" its NDA.

First, under 21 CFR 60.3(b)(12),[43] the agency defined the term "marketing application" as an application for:

(i) Human drug products ***submitted*** under section 505(b) of the Act or section 351 of the Public Health Service Act;
(ii) Medical devices ***submitted*** under section 515 of the Act;
(iii) Food and color additives ***submitted*** under section 409 or 721 of the Act; or
(iv) Animal drug products ***submitted*** under section 512 of the Act.

In each instance, the agency could have included in the definition of a marketing application language recognizing that the application must be one that FDA has "filed." It did not.

Second, under 21 CFR 60.22, FDA defined the statutory phrase "initially submitted" without reference to the agency's NDA filing standard under 21 CFR 314.101. Under the NDA regulations, an application is filed if the agency makes a threshold finding that it is "sufficiently complete to permit a substantive review."[44] Under the PTE regulations, in contrast, an application is "*initially submitted*" if it contains "sufficient information to allow FDA to commence review of the application."[45] There is no reference to "filing" and no reference to "completeness" in the standard FDA established under the PTE regulations.

By its careful choice of words, the agency established a standard different from the administrative filing standard. The "initially submitted" standard is based on whether the sponsor has provided the agency with sufficient information to start its review. It is not conditioned on the submission of a "complete" application. In fact, in the course of promulgating the PTE rules, FDA explained that an application could be "initially submitted" even "[i]f the agency requires additional information after beginning its review."[46] Again, the focus is on the true start of the review of the application, and not on whether the application meets a separate standard – one not even referenced in the regulations – for administrative filing.

Thus, when given the opportunity to define the statutory terms "application" and "initially submitted" under section 156(g)(1)(B), the agency declined to incorporate its standard for administrative filing. Instead, the agency followed the lead of the statute and based its regulatory framework for making PTE determinations on the sponsor's act of submitting an application and on whether the agency in fact could begin its review activities. For the agency now to base its decision on whether the Pradaxa NDA was accepted for filing in its original form is arbitrary, capricious, and not in accord with the governing statute or the agency's own

[43] 21 CFR 60.3(b)(12) (emphasis added).

[44] 21 C.F.R. § 314.101(a)(1).

[45] 21 C.F.R. § 60.22(f) (emphasis in original).

[46] Patent Term Restoration Regulations, 53 Fed. Reg. 7298, 7302 (Mar. 7, 1988).

regulations.

C. FDA's Actions and Statements Show that the Agency was Actively Reviewing the Pradaxa NDA from Before December 2009 through April 2010

According to the April 19 decision, BIPI's initial NDA submission did not trigger the beginning of the approval phase because it was "incomplete." Instead, the agency insists that the "complete" NDA was submitted on April 19, 2010. In fact, all the elements required under section 505(b)(1) for an NDA were submitted to the agency as of December 15, 2009. The NDA, as initially submitted, plainly contained "sufficient information to allow FDA to commence review of the application."[47]

The agency's own actions from December 2009 through April 2010 show that it was engaged in an intense and broad-based review of the Pradaxa NDA. Indeed, because FDA had invited BIPI to submit the application on a "rolling" basis, intensive review activity was already underway by the time the last elements of the NDA were submitted on December 15, 2009. When one considers (1) the number of FDA experts involved in the review of the application during this period; (2) the frequency, quality, and breadth of the exchanges between FDA reviewers and the BIPI team; and (3) the agency's own characterization of its actions during this period, there can be no doubt that the NDA – as of December 2009 – contained "sufficient information" to allow the agency to "commence" its review.[48]

In the period immediately prior to the "initial submission" of the application and thereafter, FDA clearly had commenced its substantive review:

November 2009

- Review Division requests the Division of Biometrics to assist in the review of the carcinogenicity data for dabigatran.[49]

- Review Division requests that OSE initiate its review of the carton and container labels for dabigatran and complete its review by March 15, 2010.[50]

December 2009

- Review Division requests the biopharmaceutics experts in the Office of New

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[47] 21 C.F.R. § 60.22(f).

[48] *Id.*

[49] Tab 14, Request for Consultation from A. Blaus to K. Lin, Division of Biometrics (Nov. 12, 2009).

[50] Tab 15, Request for Consultation from A. Blaus to OSE (Nov. 16, 2009).

Drug Quality Assessment begin their review of the dissolution method and specifications for the products, and the *in vitro* data to support marketing of the commercial batch of the drug product.[51]

- Review Division requests that OSE begin review of the Risk Evaluation and Mitigation Strategies for the product.[52]

- Review Division requests that experts in the Division of Drug Marketing, Advertising, and Communications begin their review of the draft labeling of the product.[53]

January 2010

- Review Division requests an environmental consult from the Office of Pharmaceutical Science to review the ecotoxicity and environmental data provided in the Environmental Assessment Report for the NDA.[54]

February 2010

- FDA's Division of Medication Error Prevention and Analysis ("DMEPA") completes its analysis of the packaging and appearance of Pradaxa capsules and provides comments to BIPI.[55]

- Review Division sends BIPI detailed requests from the agency's liver toxicity requests, with assurances to the company that "regardless of the RTF, we are continuing our review of the application."[56]

- FDA's Executive Carcinogenicity Assessment Committee ("CAC") meets to consider BIPI's rat and mice carcinogenicity studies.[57]

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[51] Tab 16, Request for Consultation from D. Henry to P. Marroum, ONDQA (Dec. 3, 2009).

[52] Tab 17, Request for Consultation from A. Blaus to OSE and N. Ton (Dec. 16, 2009).

[53] Tab 18, Request for Consultation from A. Blaus to W. Amchin, DDMAC (Dec. 16, 2009).

[54] Tab 19, Request for Consultation from D. Henry to R. Bloom, OPS/PARS (Jan. 11, 2010).

[55] Tab 15, Request for Consultation from A. Blaus to OSE (Nov. 16, 2009); *see also* e-mail correspondence, on file at FDA, dated Feb. 4, Mar. 1, and Mar. 15, 2010.

[56] Tab 9, E-mail from A. Blaus, FDA Project Manager, to M. Kliewer (Feb. 16, 2010).

[57] Tab 20, Meeting Minutes from D. Jacobson-Kram, Chair, Executive CAC (Feb. 16, 2010).

March 2010

- BIPI submits plan in response to DMEPA comments (on Mar. 1, 2010) and the Review Division concurs with the plan (Mar. 15, 2010).[58]

- FDA's Division of Biometrics completes is statistical review of the carcinogenicity studies in NDA 22512.[59]

Even when FDA prepared its final review documents in October 2010, agency reviewers acknowledged that they continued with their review after the RTF Letter was issued. For example, according to FDA's Office of New Drug Quality Assessment Division Director's Memo, dated October 18, 2010:

> The original submission of this rolling 505(b)(1) NDA was received 15-DEC-2009 from Boehringer Ingelheim Pharmaceuticals, Inc., of Ridgefield, Connecticut. The drug substance is a new molecular entity (NME). The 15-DEC-2009 submission was refused to file (RTF) on 12-FEB-2010 for clinical reasons. ***However, due to the priority / rolling status of the application, the CMC review remained ongoing after the RTF.*** The application was resubmitted on 19-APR-2010 and was granted priority review status.[60]

Boehringer Ingelheim does not have a complete window into all of the agency's activities with respect to the Pradaxa NDA during this period. But even based on the type and frequency of the interactions to which it was privy, it is beyond dispute that review of the application had commenced as of the time BIPI completed its rolling review submission in December 2009. This review continued without interruption following issuance of the RTF Letter. The substance of the activity, and the form of communication, bore all of the signposts of a fully engaged NDA review. Finally, once review of the application began, the "approval phase" for PTE purposes was triggered and the agency had no basis to revert back to the testing phase.[61]

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[58] Tab 15, Request for Consultation from A. Blaus to OSE (Nov. 16, 2009); *see also* e-mail correspondence from N. Ton, on file at FDA, dated March 15, 2010.

[59] Tab 21, CDER, Pradaxa Statistical Review and Evaluation Carcinogenicity Study, Memo from S. Thomson and K. Lin 40 (Mar. 8, 2010) (concurring with primary review on Mar. 9, 2010).

[60] Tab 10, Excerpt of CDER PRADAXA CHEMISTRY REVIEW, ONDQA Division Director's Memo 1 (emphasis added). Full Chemistry Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000ChemR.pdf.

[61] Determination of Regulatory Review Period for Purposes of Patent Extension; Tonocard Tablets, 50 Fed. Reg. 19,809-10 (May 10, 1985) (finding that issuance of a "not approvable" letter that required additional clinical testing by the NDA sponsor did not interrupt the approval phase as long as the sponsor had made "a deliberate effort to submit an application containing all information necessary for agency review to begin").

D. The Requested Relief Does not Require a Change in FDA Policy

As detailed above, the patent term extension statute unambiguously states that the approval phase begins on the date the application for the approved product was "initially submitted" under section 505 of the FDCA.[62] We appreciate the concern the agency may hold that an overly literal reading of the statute might allow an aggressive NDA applicant to prematurely trigger the start of the "approval phase" by submitting a facially incomplete application – one so deficient that it does not allow the agency to commence its review.

The agency, however, already has the authority to guard against such strategies. To prevent sponsors from prematurely triggering the approval phase, FDA further defined the "initially submitted" standard in its implementing regulations. Under the agency's regulations, an NDA is considered "initially submitted" when it "contains sufficient information to allow FDA to commence review of the application."[63] If a sponsor submits a facially deficient NDA, the agency need only resolve not to commence its substantive review of the application and the approval phase will not be triggered.

In most cases, an NDA that has been refused is held in abeyance; all activity on the application is halted for fear of wasting agency resources on an application that may materially change or may never be put into a reviewable form. Boehringer Ingelheim agrees with FDA that these applications should not be considered initially submitted until they have been resubmitted with sufficient information to allow the agency to commence its review.[64]

Boehringer Ingelheim's case is entirely different because the agency, by its own admission, resolved to continue the review of the Pradaxa NDA despite its refusal to file the application. In particular:

- This was not a standard NDA submission; it was submitted for review on a rolling basis at FDA's request, to allow FDA to complete its work on a timely basis.

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[62] 35 U.S.C. § 156(g)(1)(B).

[63] 21 C.F.R. § 60.22(f).

[64] FDA has previously considered the effect of an RTF decision on the initial submission date when it determined the regulatory review period of Pravachol®. Tab 22, Letter from Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, FDA, to Terry Coleman, Esq., Fox, Bennett & Turner (Jan. 27, 1994). With Pravachol, FDA found that the date of initial submission was when the Pravachol NDA was resubmitted following an RTF decision. Pradaxa's regulatory review period can be readily distinguished, however, because of Boehringer Ingelheim's extensive record of substantive agency review following the RTF decision and prior to NDA resubmission. In contrast, Pravachol's sponsor presented no evidence of substantive review during the same corresponding time period besides "informal communications" over the course of "two meetings and two telephone calls."

- This was not a typical new drug review, to the extent that the agency's substantive review began before all the NDA modules had been submitted; the review proceeded after the RTF Letter was issued; and it continued without pause until the NDA was approved.

- This was not a routine RTF. Rather, this was one of the rare situations described in FDA's guidance where, for particularly critical drugs, FDA will continue to "review parts of a refused application if it believes that initiating the full review at the earliest possible time will better advance the public health."[65]

- Finally, the Pradaxa NDA – as it existed in December 2009 – contained "sufficient information to allow FDA to commence review of the application,"[66] thus meeting the statutory standard for the initiation of the approval phase.

By granting the requested relief in this case, FDA will not be foreclosed from delaying the start of the PTE approval phase for those facially deficient NDAs for which it cannot commence review. Nor is it likely that sponsors will begin submitting "placeholder" NDAs simply to trigger the start of the approval phase for PTE purposes. Refuse to file decisions generally cause substantial delays in the overall time to approval of a new drug application. Sponsors have every incentive to get their drugs to market as quickly as possible. Even day-for-day patent term extensions provide only partial compensation for regulatory delays because those delays still postpone the sponsor's recovery on its investment and create the risk that competing drugs will emerge or gain market share.

Finally, the statute and FDA's regulations contain safeguards against deliberate efforts to enlarge the approval phase through the submission of facially deficient applications. A patent term extension is reduced by any periods of time during which it is shown that the applicant "did not act with due diligence."[67] Due diligence is defined as the "degree of attention, continuous directed effort, and timeliness as may reasonably be expected from, and are ordinarily exercised by, a person during a regulatory review period."[68] In the unlikely event that an applicant sought to manipulate the system by delaying FDA's review during the approval phase, it would receive no patent term extension for the periods attributable to its delay. Accordingly, there is little risk that sponsors will be able to trigger the start of the approval phase by submitting grossly incomplete applications.

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[65] CDER, NEW DRUG EVALUATION GUIDANCE DOCUMENT: REFUSAL TO FILE 3 (July 12, 1993) (emphasis added).

[66] 21 C.F.R. § 60.22(f).

[67] 35 U.S.C. § 156(c)(1); 21 C.F.R. § 60.30.

[68] 35 U.S.C. § 156(d)(3).

IV. CONCLUSION

Agency review of the Pradaxa NDA began no later than the initial submission of the full NDA in December 2009. Under the governing law and precedent, the agency has no basis to revert back to the testing phase.

FDA's regulatory review determination of Pradaxa cannot be reconciled with the text of the statute, the legislative history, the policy underlying patent term extension, and the agency's own regulations. Nor can the agency's determination be reconciled with the record and undisputed facts that: (1) the final documents completing the Pradaxa NDA were submitted on December 15, 2009; (2) FDA's review of the NDA continued without interruption from before December 15, 2009, until the product was approved on October 19, 2010; and (3) the Division itself explicitly acknowledged that it would continue its review of the NDA after the issuance of the RTF Letter.

For these reasons, Boehringer Ingelheim requests that FDA revisit its earlier determination, recalculate the regulatory review period for Pradaxa, and conclude that the Pradaxa NDA was "initially submitted" on the date the final documents of the application were submitted for FDA's rolling review – December 15, 2009. This correction would yield a patent term extension of 1,471 days, an increase of roughly two months more than the extension that would result from FDA's original determination.

On behalf of Boehringer Ingelheim, I would like to thank you for your careful consideration of this request.

Sincerely,

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